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Comparison of resected lymph nodes and additional factors in colorectal cancer patients undergoing emergency versus elective surgery

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ABSTRACT

Aims: Controversy persists regarding the number of lymph nodes (LNs) that should be removed during surgery for accurate colorectal carcinoma (CRC) staging and its impact on prognosis. The effects of other prognostic factors on survival, such as the metastatic LN to resected LN (LNR) ratio and the type of surgical approach, were retrospectively examined.

Methods: A total of 325 patients who underwent emergency or elective surgery for CRC between March 1st, 2019, and December 31st, 2022, were included in the study. Age, sex, tumor location, stage, number of resected LNs, number of metastatic LNs, presence of distant metastases, distance of the tumor from the surgical margins, need for ostomy opening, development of postoperative complications, and level of tumor markers at diagnosis were recorded for patient records.

Results: The data of 142 (43.7%) emergency surgery patients and 183 (56.3%) elective surgery patients were compared. It was revealed that there was a positive relationship between the removal of at least 22 LNs during surgery and survival (p=0.036). Factors such as age, a high LNR, emergency surgery, advanced stage of CRC, and not receiving adjuvant chemotherapy were significant predictors of increased mortality (age: hazard ratio (HR): 1.03, 95% CI: 1.01-1.05, p<0.001; LNR: HR: 4.74, 95% CI: 1.69-13.3, p=0.003; emergency surgery: HR: 2.33, 95% CI: 1.51-3.59, p<0.001; advanced stage: HR: 3.24, 95% CI: 1.81-5.79, p<0.001; adjuvant chemotherapy: HR: 4.93, 95% CI: 2.94-8.25, p<0.001) in the patients with CRC.

Conclusion: Patients with CRC, who had fewer LN dissections, perforation-related peritonitis, advanced disease, were not receiving adjuvant chemotherapy, and emergency surgery, had a worse prognosis.

Keywords: Colorectal cancer, lymph node, ratio, prognosis, survival, surgery

INTRODUCTION

In staging colorectal carcinoma (CRC), the optimal number of lymph nodes (LNs) to be examined is still debatable. Although the guidelines suggest a minimum of 12 LN resections for staging, it is recommended that as many LNs as possible be harvested.[1] In all of the histologic staging methods, LN metastases are crucial for staging colorectal tumors.[2,3] Due to the unreliability of the data, current staging systems still need to be improved, with disease recurrence occurring in approximately 20%-25% of patients without proven LN metastases.[4] The most critical factors determining the number of LNs removed in colorectal cancer surgery are the operating surgeon and the pathologist who examines the specimen.[5] Studies performed on patients with stage II tumors have shown that the more LNs dissected, the easier it is to identify the LN-negative patient group.[6] The metastatic LN to dissected LN ratio (LNR) is another factor associated with prognosis.[7] The number of LNs reported in the pathology report is influenced by the type of surgery (such as left or right hemicolectomy) and pathological examination (such as the pathologist's experience and interest). In addition, the location and number of tumors the patient has and the types of tumors are other factors that affect the number of LNs removed.[8] The number of LNs removed is related to the tumor stage, tumor size, and tumor location in the colon.[9] In CRC patients, it is recommended that at least 15 LNs be removed to identify positive LNs and determine an accurate stage of the disease. In metastatic patients, at least 21 LNs should be removed.[10,11] Some researchers have emphasized that extensive LN dissection may provide better local-regional control, eliminate undetectable lesions, and possibly, prolong survival.[12,13] However, another study suggested that extensive LN dissection may increase the risk of postoperative comorbidity without improving survival.[14] Nowadays, discussions about the number of dissected LNs, the LNR, and their impact on prognosis continue. In this study, the relationship between the number of resected LNs, metastatic

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LNs, and the LNR with prognosis was investigated in patients who underwent emergency and elective surgery due to CRC. Our secondary aims were to investigate the effects of patient age, the ratio of metastatic lymph nodes to the total lymph nodes removed, the stage of the disease, and chemotherapy on survival, which we believe are effective on prognosis in the early period after CRC surgery.

METHODS

The study was initiated after approval by the Ankara Bilkent City Hospital No 1 Clinical Researches Ethics Committee (Date: 26.04.2023, Decision No: E1-23-3492). Our study was conducted in accordance with the Declaration of Helsinki. A total of 406 patients aged 18 years and older who underwent emergency or elective surgery for CRC at the Department of General Surgery between March 1st, 2019, and December 31st, 2022, were enrolled in the study. 81 patients who did not meet the study inclusion criteria were excluded from the study. The patients' records were retrospectively reviewed. It was found that 142 patients with CRC had undergone emergency surgery. These patients were included in the study. The control group included 183 CRC patients who had undergone elective surgery by surgeons participating in the study. The length of hospital stay (LOHS), postoperative follow-up duration, and patients' survival during follow-up were recorded. The age, sex, location, stage of CRC, number of LNs removed during surgery, number of metastatic LNs, presence of distant metastases, distance of the tumor from the surgical margins, placement of colostomies, development of postoperative complications, and level of tumor markers at the time of diagnosis were extracted from the patients' records and recorded.

In our hospital, CRC surgeries are performed as complete mesocolic excision (CME) and total mesorectal excision (TME) in every possible case. This also applies to patients undergoing emergency surgery. However, in certain emergency cases, performing CME and TME is impossible. This study retrospectively examined the factors affecting the prognosis of CRC patients who underwent emergency and elective surgery.

Statistical Analysis

IBM SPSS Statistics for Windows 25.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analyses. Descriptive statistics, including frequencies and percentages, were obtained for the categorical variables. Normal distribution of the data between groups was analyzed using the Kolmogorov-Smirnov test. The Chi-squared test was used for analysis of the categorical variables. The significance of differences between groups for noncategorical variables was assessed with the Mann-Whitney U test. To determine the minimum number of LNs that must be removed to make a significant contribution to survival, a receiver operating characteristic (ROC) curve was constructed to determine the cut-off value. The Kaplan-Meier method was used to calculate the mean survival. Cox proportional hazard regression analysis was performed to estimate hazard ratios (HRs) for CRC-specific mortality. Results were considered statistically significant at $p<0.05$.

RESULTS

The study included 325 patients, of whom 142 (43.7%) underwent emergency surgery and 183 (56.3%) underwent elective surgery for CRC. The mean age of the emergency surgery patients was 67.99±13.22 years, while it was 65.48±12.41 years for the elective surgery patients (p=0.103). Of the CRC surgery patients, 202 (62.2%) were male and 123 (37.8%) were female. The median follow-up time of the emergency surgery patients was 19.5 months (interquartile range (IQR) 25: 4, IQR 75: 30), and that of the elective surgery patients was 27 months (IQR 25: 21, IQR 75: 42). The follow-up period of the emergency surgery patients was significantly shorter due to higher mortality [(34/183) 18.6% vs (57/142) 40.1%] ($p<0.001$). The tumor localization and surgical operations performed in the patients with CRC who were operated on under emergency and elective conditions are shown in Table 1.

Table 1. Tumor localization and surgical operations performed in the CRC patients operated on under emergency and elective conditions

	Type of surgery	
Tumor localization	**Elective [n (%)]**	**Emergency [n (%)]**
Rectum+sigmoid	25 (13.7)	30 (21.1)
Right colon	126 (68.85)	85 (59.9)
Left colon	29 (15.8)	25 (17.6)
Transverse colon	1 (0.55)	1 (0.7)
Other	2 (1.1)	1 (0.7)
The surgery performed		
Sigmoid resection	13 (7.1)	19 (13.4)
Anterior resection	1 (0.55)	8 (5.6)
Low anterior resection	9 (4.9)	2 (1.4)
Abdominoperineal resection	2 (1.1)	1 (0.7)
Left hemicolectomy	27 (14.8)	24 (16.9)
Right hemicolectomy	115 (62.8)	83 (58.4)
Transverse colectomy	1 (0.55)	1 (0.7)
Subtotal colectomy	11 (6)	3 (2.1)
Other	4 (2.2)	1 (0.7)
TNM stage		
Stage I	11 (6)	5 (3.5)
Stage II	75 (41)	46 (32.4)
Stage III	74 (40)	61 (43)
Stage IV	23 (13)	30 (21.1)
Distribution of patients who died according to colectomy		
Right hemicolectomy	22 (64.7)	32 (56)
Left hemicolectomy	5 (14.7)	12 (21)
Rectum and sigmoid colon resection	5 (14.7)	9 (16)
Other	2 (5.9)	4 (7)

n: Number of patients, %: Percentage, CRC: Colorectal carcinoma, TNM: Tumor size (T), lymph node involvement (N) and distant metastasis (M)

The median number of resected LNs was 19 (IQR 25: 13, IQR 75: 28,5) in the emergency patients and 21 (IQR 25: 16, IQR 75: 29) in the elective patients. The median number of metastatic LNs was 1 (IQR 25: 0, IQR 75: 4) in the emergency patients and 0 (IQR 25: 0, IQR 75: 3) in the elective patients. Only 4 of the patients were given neoadjuvant chemotherapy,

3 of whom were in the elective surgery group and 1 of whom underwent emergency surgery because colon perforation developed while receiving chemotherapy. The elective surgery patients had a significantly higher number of LN dissections of 12 or more than the emergency surgery patients (p=0.017) in Table 2.

There were no significant differences between the groups regarding LN metastasis and the development of postoperative complications (p=0.515 and p=0.129, respectively). However, patients with CRC who underwent emergency surgery had a significantly higher rate of distant organ metastasis (p=0.007). A significantly higher rate of ostomy opening was observed the emergency surgery patients than the elective surgery patients (p<0.001). Evaluation of the disease stage revealed that the emergency surgery patients were at a more advanced stage (p=0.045). The mortality rate was significantly higher in the emergency surgery patients (Kaplan-Meier test value: 21.648, log rank p<0.001). Emergency surgical intervention, LN metastasis, bowel perforation, need for ostomy, and advanced disease increased mortality, removal of 22 or more LNs, and administration of adjuvant chemotherapy

Table 2. Comparison of selected parameters in patients undergoing emergency and elective surgery

			Type of surgery		
			Elective	Emergency	p value
Ostomy opening	No	n	159	66	<0.001
		%	70.7	29.3	
	Yes	n	24	76	
		%	24	76	
Distant organ metastasis	No	n	158	106	0.007
		%	59.8	40.2	
	Yes	n	25	36	
		%	41	59	
Lymph node metastasis	No	n	91	67	0.515
		%	57.6	42.4	
	Yes	n	88	75	
		%	54	46	
Postoperative complication	No	n	175	130	0.129
		%	57.4	42.6	
	Yes	n	8	12	
		%	40	60	
Number of LNs removed	<12	n	16	25	0.017
		%	39	61	
	≥12	n	167	117	
		%	58.8	41.2	
Colectomy	Right hemicolectomy	n	128	86	0.077
		%	59.8	40.2	
	Other	n	55	56	
		%	49.5	50.5	
Stage of the disease	Early stage	n	86	51	0.045
		%	62.8	37.2	
	Advanced stage	n	97	91	
		%	51.6	48.4	
Adjuvant chemotherapy	No	n	89	72	0.711
		%	55.3	44.7	
	Yes	n	94	70	
		%	57.3	42.7	
Overall survival	Alive	n	149	85	<0.001*
		%	63.7	36.3	
	Died	n	34	57	
		%	37.4	62.6	
Total		n	183	142	
		%	56.3	43.7	

Pearson Chi-square test was used, *Kaplan-Meier test used, n= Number of patients, LNs: Lymph nodes

were significantly associated with a decrease in mortality (p<0.001, p=0.003, p=0.005, p<0.001, p<0.001, p=0.036, and p<0.001, respectively) in Table 3. Tumor markers (CEA, CA19-9) in the preoperative blood samples were significantly higher in the emergency surgery patients compared to the elective surgery patients (p<0.001 and p<0.001, respectively). There was no significant difference between the emergency and elective surgery patients in terms of the distance of the tumor to the proximal and distal resection margins (p=0.339 and p=0.239, respectively). When considering survival, the number of LNs removed was significantly higher, and the LNR value was considerably lower in the surviving patients (p=0.047 and p<0.001, respectively) in Table 4. The ROC curve analysis showed that the removal of at least 22 LNs was significantly positively associated with survival [area under the ROC curve (AUC): 59.4%]. The sensitivity of removing at least 22 LNs to predict better survival was 78.8% and the specificity was 65.9%. The LOHS was extended for the elective surgery patients (p=0.002). The median LOHS for the elective surgery patients was 11 days (IQR 25: 8, IQR 75: 15), while for the emergency surgery patients, it was 9 days (IQR 25: 6, IQR 75: 15). This difference was attributed to the higher early postoperative mortality in the emergency surgery patients and the hospital admission of the elective surgery patients during the preoperative preparation phase. When multivariate Cox regression analysis was performed to determine the factors affecting mortality in the CRC patients, it was determined that increasing age, having surgery under emergency conditions, advanced stage of the disease in Figure, and a high LNR increased mortality, while receiving adjuvant chemotherapy decreased mortality (age: HR: 1.03, 95% CI: 1.01-1.05, p<0.001; LNR: HR: 4.74, 95% CI: 1.69-13.3, p=0.003; emergency surgery: HR: 2.33, 95% CI: 1.51-3.59, p<0.001 advanced stage: HR: 3.24, 95% CI: 1.81-5.79, p<0.001; adjuvant chemotherapy: HR: 4.93, 95% CI: 2.94-8.25, p<0.001) in Table 5.

Table 3. Distribution of the data based on whether the patients survived or not

			Survival		
			Alive	Died	p value
Surgery	Emergency operation	n	85	57	<0.001
		%	59.9	40.1	
	Elective operation	n	149	34	
		%	81.4	18.6	
Perforation	No	n	221	77	0.005
		%	74.2	25.8	
	Yes	n	13	14	
		%	48.1	51.9	
Ostomy	No	n	184	41	<0.001
		%	81.8	18.2	
	Yes	n	50	50	
		%	50	50	
LN metastasis	No	n	129	32	0.003
		%	80.1	19.9	
	Yes	n	105	59	
		%	61	39	
Number of LNs removed	<12	n	25	16	0.271
		%	68.3	31.7	
	≥12	n	209	75	
		%	73.6	26.4	
Number of LNs removed	<22	n	119	60	0.036
		%	66.5	33.5	
	≥22	n	115	31	
		%	78.8	21.2	
Adjuvant chemotherapy	No	n	91	70	<0.001
		%	56.5	43.5	
	Yes	n	143	21	
		%	87.2	12.8	
Stage of the disease	Early	n	117	20	<0.001
		%	85.4	14.6	
	Advanced	n	117	71	
		%	62.2	37.8	
Total		n	234	91	
		%	72	28	

Kaplan-Meier test used, n= Number of patients, LN= Lymph node, LNs: Lymph nodes

Table 4. Impact of the LN count and LNR on overall survival in the CRC patients

Survival		n (%)	Mean rank	p value
Number of LNs removed	Alive	234 (72)	171.53	0.047
	Died	91 (28)	141.07	
LNR	Alive	234 (72)	147.37	<0.001
	Died	91 (28)	203.19	
CEA	Alive	234 (72)	136.71	<0.001
	Died	91 (28)	230.60	
CA 19.9	Alive	234 (72)	146.37	<0.001
	Died	91 (28)	205.77	

Kaplan-Meier test was used, n= Number of patients, LN= Lymph node, LNR= The ratio of metastatic lymph nodes to the number of dissected lymph nodes, CRC: Colorectal carcinoma, LNs: Lymph nodes, CEA, CA19-9: Tumor markers

Table 5. Analysis of the factors influencing the HR in the CRC patients

		95.0% CI for exp (B)		
	HR	Lower	Upper	p value
Age	1.03	1.01	1.05	<0.001
LNR	4.74	1.69	13.3	0.003
Emergency/elective	2.33	1.51	3.59	<0.001
Early/advanced	3.24	1.81	5.79	<0.001
Adjuvant chemotherapy	4.93	2.94	8.25	<0.001

The Cox regression test was used. X =144.890, p<0.001, HR= Hazard ratio, CRC: Colorectal carcinoma, LNR= The ratio of metastatic lymph nodes to the number of dissected lymph nodes

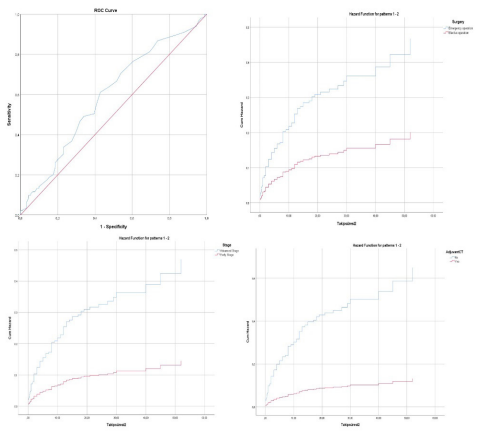

Figure. Flow chart of exclusion criteria

DISCUSSION

The primary results of this study were that although our clinic pays attention to performing CME and TME in every possible CRC patient, the number of LNs removed in patients undergoing emergency surgery remains low. Mortality was higher in the emergency surgery patients, especially in those with tumor perforation and extensive peritonitis. The secondary results of this study were that factors such as advanced age, urgent surgical intervention, a high LNR rate, not receiving adjuvant chemotherapy, and advanced disease were the main determinants of increased mortality in patients with CRC.

Nelson et al.[15] reported that LN positivity could be accurately determined in 80%-90% of patients by examining 12 LNs. Feng et al.[16] suggested that the optimal number of LNs to examine for prognostic classification in LN-negative colon cancer should be 15. Wu et al.[17] reported that resecting at least 20 LNs in patients with right-sided colon tumors was superior to the recommended minimum of 12 LN resections for accurate staging, and that performing less than 20 LN resections was a poor prognostic indicator. On the other hand, Lee et al.[18] reported that having a minimum of 22 resected LNs in right-sided colon tumors improved overall survival. In their recent study, Hayes et al.[19] reported that resecting more LNs in LN-negative patients improved overall survival but did not have a significant association with increased overall survival in the presence of LN metastasis. Lacy et al.[20] reported that optimal oncological surgery for middle and lower rectal cancers, performing TME to ensure removal of the tumor and locoregional LNs, was directly linked to local recurrence and survival outcomes. Benz et al.[21] reported that complete mesocolon excision had no general benefit in stage I and II right-sided colon cancers and that overall survival was better in stage III disease. In contrast to researchers advocating for increased LN resection, Li Destri et al.[22] suggested that the immune status of patients could be adversely affected by an increase in the number of excised LNs and that increasing the number of excised LNs may be ineffective in improving survival in patients with metastasis. The current study showed that the overall survival rate was positively affected in patients who had 22 or more LNs removed. This may indicate that more LN dissection has a positive effect on prognosis, and it also shows that it is possible to perform more LN dissections due to the early stage of the disease. In addition, an urgent need for surgery arises in advanced-stage tumors due to obstruction and perforation. Distension and inflammation in the intestines of these patients complicate LN dissection. Particularly in stage III CRC patients, it has been reported that using the LNR instead of the number of resected LNs provides a better prognosis.[22] The present study found that patients with a low LNR had a higher survival rate, and a significant relationship was found between the LNR and prognosis.

The incidence of colon perforation in patients undergoing emergency surgery ranges from 18.6% to 28.4%.[23,24] These patients have a lower survival rate, a higher need for ostomy, and higher rates of recurrence and distant organ metastasis.[24,25] In patients who undergo surgery for colon perforation, the presence of local recurrence and distant metastasis are higher than in those who undergo surgery for obstruction, while disease-free survival is lower.[25] Perforated CRC cases are often associated with fewer resected LNs than in patients with obstructive disease.[25,26] Patients undergoing surgery due to colon perforation experience more postoperative complications and extended LOHS in the intensive care unit than those operated on for obstruction.[27] In this study, patients with unresectable tumors in the colon or rectum who only had an ostomy were excluded from the study. The ostomy of the patients included in the study was in the form of a diverting ostomy or a Hartmann procedure. Most of these patients had colon perforation and widespread peritonitis. Patients who underwent surgery due to colorectal cancer perforation had fewer lymph node resections and had poorer survival rates.

While planning this study, we planned to investigate the factors affecting early survival of CRC patients who underwent emergency and elective surgery. Colon cancer and rectal cancer are conditions that require different approaches. For this reason, we tried to equalize the tumor locations of the patients we included in the study in both groups as much as possible. However, the fact that patients with colon and rectal cancer were evaluated together was a limiting factor of the study.

Advanced age, female gender, emergency surgery, less than 12 resected lymph nodes, and advanced stage of CRC are negative prognostic factors. However, postoperative adjuvant chemotherapy has been shown to improve overall survival.[28,29]

In patients with colon cancer with clinical findings, advanced age, emergency surgery, advanced LN stage (N1, N2), the presence of vascular invasion, and neglect of adjuvant chemotherapy are poor prognostic factors.[30,31] In the current study, it was observed that adjuvant chemotherapy reduced local recurrence and increased overall survival because the number of patients who received neoadjuvant chemotherapy was small and the number of patients who received adjuvant chemotherapy was almost equal in patients who underwent emergency and elective surgery.

CEA and CA 19-9 are important factors that indicate the prognosis of CRC patients.[32] Additionally, elevated CA 19-9 levels before surgery are associated with a higher likelihood of postoperative recurrence.[33] In our study, tumor marker levels of CEA and CA 19-9 were found to be significantly higher in patients undergoing emergency surgery than in patients undergoing elective surgery. In addition, it was shown that among all patients, those with high CEA and CA19-9 levels had poorer survival.

The risk of death increases with advancing age in CRC patients. Patients aged 60 and above have the highest mortality risk.[34] Increased mortality risk in elderly CRC patients is influenced by comorbidities, malnutrition, low quality of life, and decreased tolerance to treatment.[35,36]

Since our hospital is a training and research hospital located in the capital, it receives a lot of referrals. For this reason, the number of patients with CRC who are operated on is very high.

Limitations

The weak aspect of the study is its retrospective design, which relies on existing data and may be subject to limitations inherent in such studies. Another weakness is that it is a single-center study. Despite the short patient follow-up

period, CRC patient data showed that the patient's age, emergency surgery, high LNR, advanced stage of the tumor, and failure to give adjuvant chemotherapy were negative prognostic factors. In addition, the vital element of this study was that it was conducted in a center with well-maintained patient records, allowing for easy access to data. This strengthened the reliability and accuracy of the information gathered for analysis.

CONCLUSION

Patients with CRC are taken in to emergency surgery because of obstruction and perforation. Patients who are born to emergency operations usually have more advanced diseases. Inflammation, peritonitis, and adhesions due to intestinal perforation make LN dissection difficult. Increasing the number of resected LNs in patients with CRC may positively affect survival. Other studies are needed to see the effects of more than 22 LN dissections on long-term mortality. Although attention is paid to performing surgery by oncological principles in our clinic, the number of LNs removed in emergency surgical operations remains low compared to that in elective surgeries due to the conditions of the surgery and advanced disease. In conclusion, factors such as advanced age, emergency surgery, high LNR rate, not receiving adjuvant chemotherapy, and advanced disease are essential determinants of increased mortality in patients with CRC.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Ankara Bilkent City Hospital No 1 Clinical Researches Ethics Committee (Date: 26.04.2023, Decision No: E1-23-3492).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Data access

The metadata for this research are available on the Zenodo site, which has a Creative Commons license-transportation link: 10.5281/zenodo.8002151.

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